# Progress in the Total Synthesis of Several Goji Berry-Pyrrole Alkaloids

Research Thesis

Presented in partial fulfillment of the requirements for graduation *with research distinction* in Chemistry in the undergraduate colleges of The Ohio State University

by

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## Abstract

Goji berries, the fruits of *Lycium barbarum* L. (Solanaceae), have become increasingly popular in the U.S. as a "super fruit" and botanical dietary supplement. Goji berry extracts have demonstrated numerous biological effects including immunomodulatory, anti-aging, and anti-cancer activities. Several amino acid-containing pyrrole alkaloids isolated from these extracts have shown potency in a quinone reductase induction assay, suggesting potential chemopreventive activity. These isolates possess similar structures, but it remains unclear what causes one to be more active than another. While it is known that each compound contains a chiral center, it is unknown what the configuration of each is. The purpose of this project was to investigate potential synthetic schemes that can be used for the total synthesis of each of the five isolated pyrrole alkaloids. The total synthesis of these compounds will allow for the determination of the stereochemical descriptors for each isolated molecule. This synthesis will be performed through the Paal-Knorr pyrrole synthesis method, which combines a saturated 1,4-diketo compound and a primary amine to form a pyrrole. The synthesized compounds will have a known stereochemistry and by comparing their optical rotation and circular dichroism with those obtained for the isolated compounds, the stereochemical descriptors can be determined. Additionally, this synthetic method will enable the interrogation of the structure activity relationship of these compounds by synthesizing both their *R* and *S* isomers, as well as novel pyrroles using additional amino acids. Several synthetic schemes have been tested in attempts to synthesize the desired pyrroles. Further studies are also being conducted which involve the use of the Maillard Reaction instead of the Paal-Knorr Pyrrole Synthesis as a method for forming the isolated pyrrole alkaloids.

**Acknowledgements**

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# Chapter 1: Introduction

## 1.1 Dietary Supplements

Botanical dietary supplements have become increasingly popular over the past decade. In 2002, 18.8% of U.S. adults reported using at least one kind of herbal or botanical dietary supplement within the past week.[1] A recent survey of dietary supplement use revealed that roughly 68% of adults are now using dietary supplements and 31% use herbal and botanical dietary supplements.[2] Of these botanicals, green tea, cranberry, garlic, ginseng, Echinacea, *Ginkgo biloba*, turmeric, and milk thistle are some of the most popular.[3] In the U.S. more than 55,000 dietary supplement products are currently on the market and 30% of global dietary supplement sales are represented.[4]

The Dietary Supplements Health and Education Act of 1994 (DSHEA) was enacted in order to establish regulations for dietary supplements that had been previously overlooked in the Federal Food, Drug, and Cosmetic Act of 1938.[5] This act defines the term "dietary supplement" and lists what a dietary supplement may contain, what it is intended for, what it may do, and what it will not include.[5] Additionally, it lists the potential hazards of dietary supplements and provides regulations for the labeling of these products.[5] The global market for dietary supplements has increased significantly since the initiation of DSHEA. In 1994, the global nutrition and supplements market was only $4 billion per year, but rose to $32 billion in 2012.[6–8]

With the increasing popularity of botanical dietary supplements, the international market for herbal products has also increased, especially in countries such as India, Japan, and China, where traditional herbal medicine has been used for centuries. In the U.S. botanical dietary supplements are commonly sold as fresh plant products, dried botanical powders, botanical extracts (liquid or dried), and purified natural compounds.[9]

Epidemiological studies have indicated a correlation between increased consumption of fruits and vegetables and a decreased risk for diseases such as hypertension, coronary heart disease, stroke, and various forms of cancer.[10] In recent years, further studies have shown the effectiveness of berries such as raspberries, strawberries, blueberries, noni, acai and goji berries in inhibiting tumor progression *in vivo*.[11] While some of these berries are already sold as botanical dietary supplements, purification and synthesis of the active compounds in these fruits could lead to more effective dietary supplements.

## 1.2 Goji Berries

Goji berries, or wolfberries, are the fruits of *Lycium barbarum* (Solanaceae). These fruits have been used in East Asia as both food and a traditional medicine for centuries. Goji berries have become increasingly popular in North America as a health food and dietary supplement. The fruits are commonly sold in the U.S. as a dried fruit, but can be eaten fresh as well. In traditional medicine, goji berries have been used to cure abdominal pain, dry coughs, fatigue, and headaches, as well as increase longevity and stop prematurely grey hair.[12]

The berries have been studied for their many health benefits, but research has focused on the antioxidant and immunomodulatory activities related to diseases such as atherosclerosis, neurodegeneration and diabetes.[13] In recent literature their chemopreventive activity was also studied, and the berries were shown to be effective in inhibiting *N*-nitrosomethylbenzylamine (NMBA)-induced tumorigenesis in the rat esophagus.[11] Additionally, studies have been done on the extracts of goji berries. The extracts of the fruits contain polysaccharides, carotenoids,

flavonoids, several vitamins, and free amino acids, as well as several other compounds with varying bioactivities.[12]

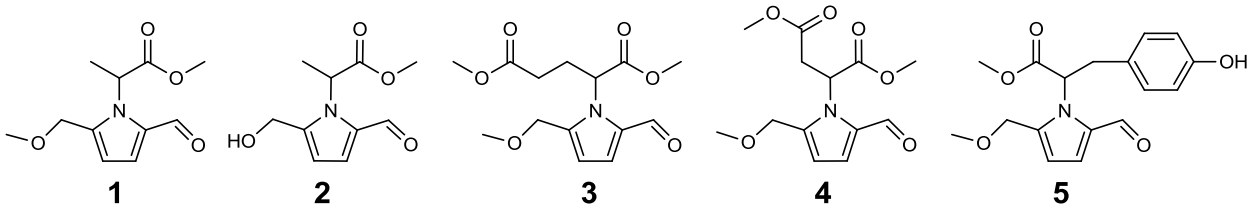



**Figure 1.1 Target compounds isolated from Goji berries**

The previous bioassay-guided fractionation of a goji berry-extracts has led to the isolation and characterization of several novel compounds that have shown activity *in vitro* with the quinone reductase-induction assay.[14] Of the active compounds, five (**1**-**5**) are pyrrole alkaloids with *N*-alkyl amino acid side chains (Figure 1.1).[14,15] Owing to the *in vitro* activity and their structural similarity, development of a method to synthesize these compounds would allow for further *in vitro* testing as well as possible *in vivo* studies. Additionally, the development of a convergent synthesis method would allow for a quantitative study of the structure-activity relationship between D and L isomers as well as pyrrole alkaloids with different *N*-alkyl side chains.

## 1.3 Paal-Knorr Pyrrole Synthesis

Five-membered heterocycles are found throughout Nature, especially in many biologically active small-molecule natural product compounds.[14] Therefore, the ability to synthesize pyrroles, furans and thiophenes is incredibly valuable in synthetic medicinal chemistry. The Paal-Knorr furan synthesis was first reported in 1884 as an acid-catalyzed

cyclization of 1,4-diketones to form furans.[16–18] This method was later modified for the synthesis of both thiophenes and pyrroles.[19]

The mechanism for this reaction (Figure **1.2**) was elucidated in 1991 by V. Amarnath et. al.[20] In this reaction, the nitrogen of a primary amine bonds with one of the carbonyl carbons.

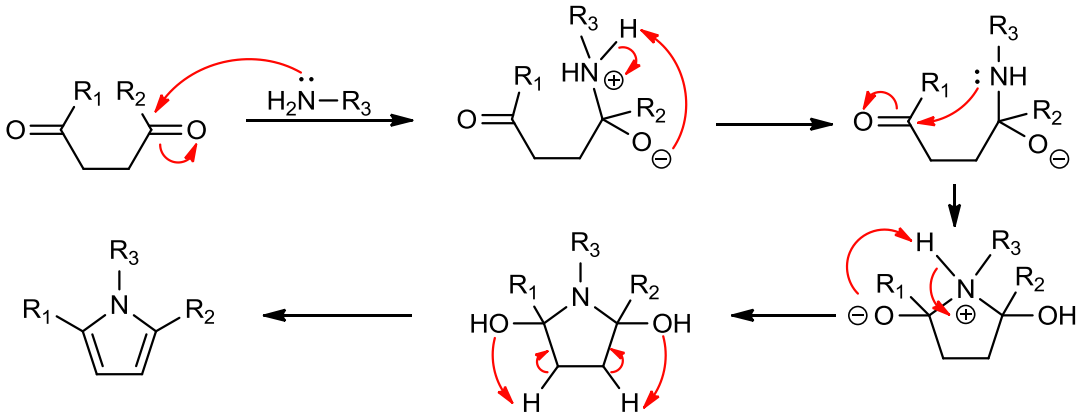



**Figure 1.2 Paal-Knorr Pyrrole Synthesis mechanism**

The oxygen is then protonated and the nitrogen bonds with the remaining carbonyl carbon and the oxygen is again protonated. The removal of water leads to the desired pyrrole compound. Additionally, V. Amarnath confirmed that the rate of reaction is affected adversely by the size of the alkyl substituents on the dione.[20] This reaction was used as the crux for the synthesis of the isolated pyrrole alkaloids, because the amino acids could potentially be used as the primary amine if a suitable 1,4-diketone compound could be synthesized as a precursor.

# Chapter 2: Synthesis of the Isolated Goji Berry Pyrrole Alkaloids

2.1 Synthetic Approach

The limited amount of each pyrrole isolated earlier from Goji berries precluded any further biological testing on the compounds.[14] In order to do further biological testing, determine the stereochemistry, and to conduct quantitative structure-activity relationship studies, it was considered that a method must be developed to synthesize these molecules.

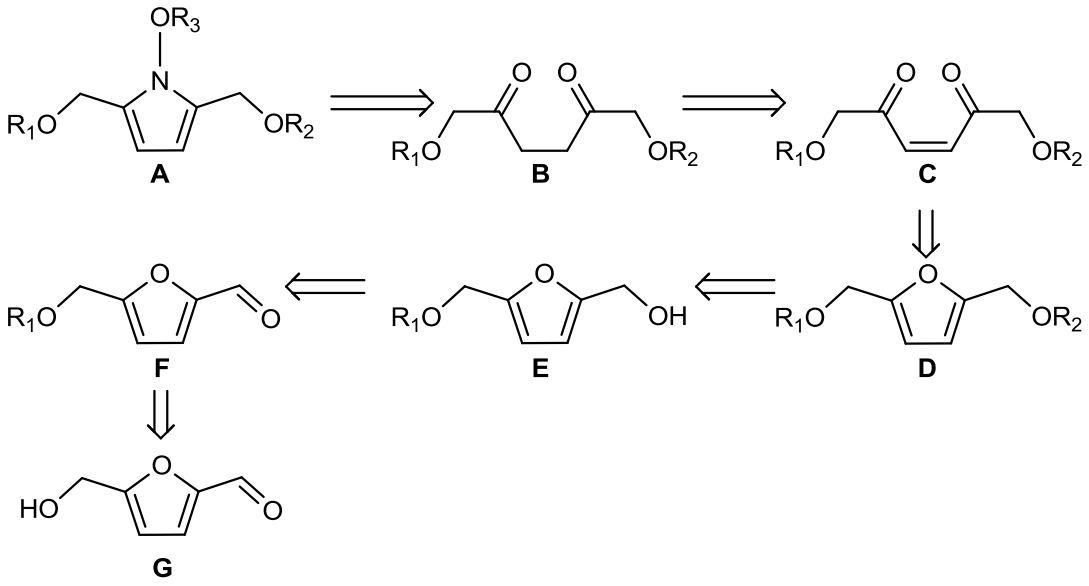



**Figure 2.1 Retrosynthetic analysis of general pyrrole compound**

The initial synthetic scheme was developed using a retrosynthetic approach (Figure 2.1). The Paal-Knorr pyrrole synthesis was used as the starting point for this retrosynthesis, and 5-hydroxymethylfurfural was considered as a possible starting material. Pyrrole **A** could be formed with an acid-catalyzed Paal-Knorr synthesis, using the saturated 1,4-diketone **B** as a starting material. Compound **B** could be formed by reducing the C-2:C-3 unsaturated bond in diketone **C**. An oxidative ring opening could be used to form saturated diketone **C** from the furan, **D**. From **D**

the protecting group $R_2$ would be removed, the primary alcohol would be converted to an aldehyde, and $R_1$ would be removed to form **E**, **F**, and **G**, respectively.

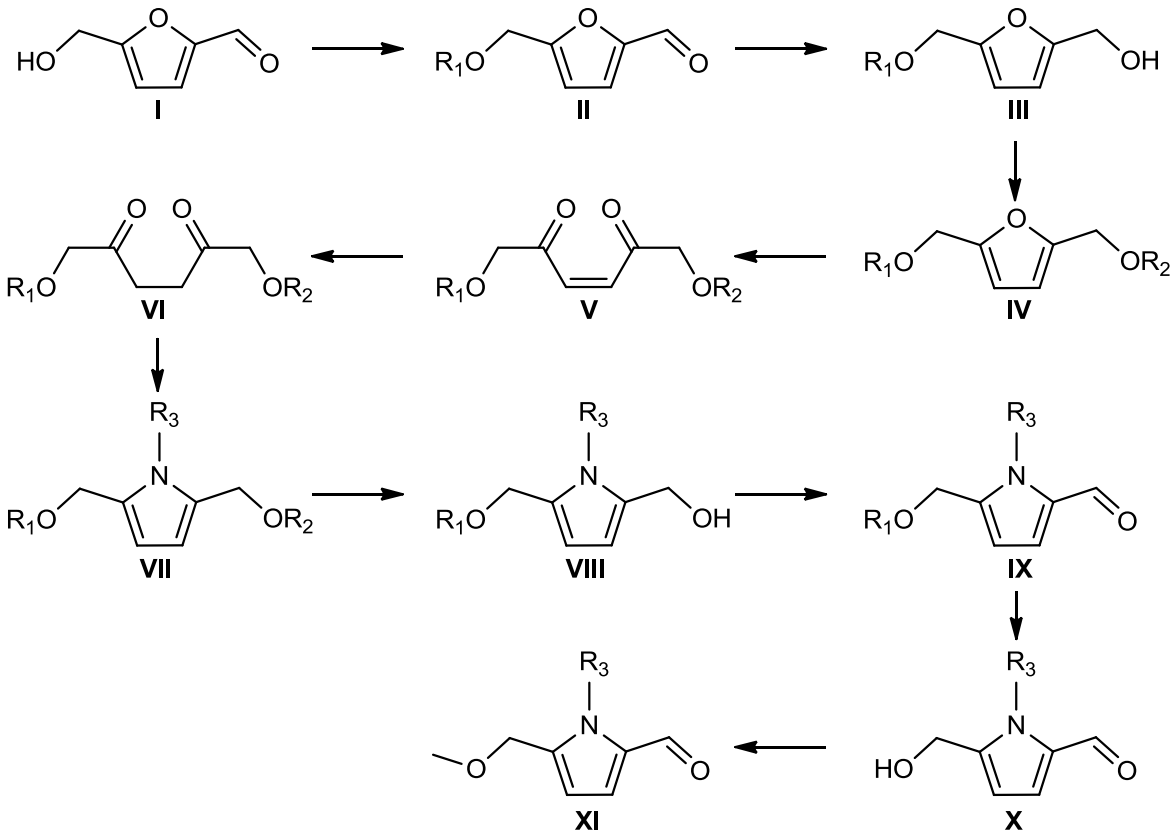



**Figure 2.2 General synthetic scheme**

From this retrosynthetic scheme, a potential synthetic method was developed (Figure 2.2). Starting with 5-hydroxymethylfurfural **I**, the first protecting group was installed on the C-5 side chain. In all of the proposed variations of this scheme, a tetrahydropyranyl (THP) ether protecting group was installed first.[21] Next, the aldehyde on the $C_2$ chain is reduced to a primary alcohol in order to install the second protecting group. This reaction is done using a sodium borohydride reduction in methanol.[22] The second protecting group is then installed on the $C_2$ side chain. This protecting group was first selected to be a *tert*-butyldiphenylsilyl (TBPS) ether,[23] but a triethylsilyl (TES) ether,[22] acetate (Ac) ester,[24] and benzyl (Bn) ether[25–27] were also installed in

different trials to form **IV**. The furan was oxidized with anhydrous *meta*-chloroperozybenzoic acid (MCPBA) to form the unsaturated 1,4-diketone **V**.[28,29] The C-2:C-3 unsaturated bond was then reduced using zinc powder in acetic acid to form **VI**.[28,29] This unsaturated diketone was used as the precursor for the Paal-Knorr pyrrole synthesis with a methoxy amino acid as the $R_3$ group.[28,30,31] Upon successful synthesis of **VII**, $R_2$ would be removed to form **VIII**, and the primary alcohol would be partially oxidized to aldehyde **IX**. The second protecting group, $R_1$, would then be cleaved to form **X**. Finally, the primary alcohol would be converted to a methoxy group to form the desired pyrrole compound.

2.2 The Use of *tert*-Butyldiphenylsilyl Ether as the $R_2$ Group

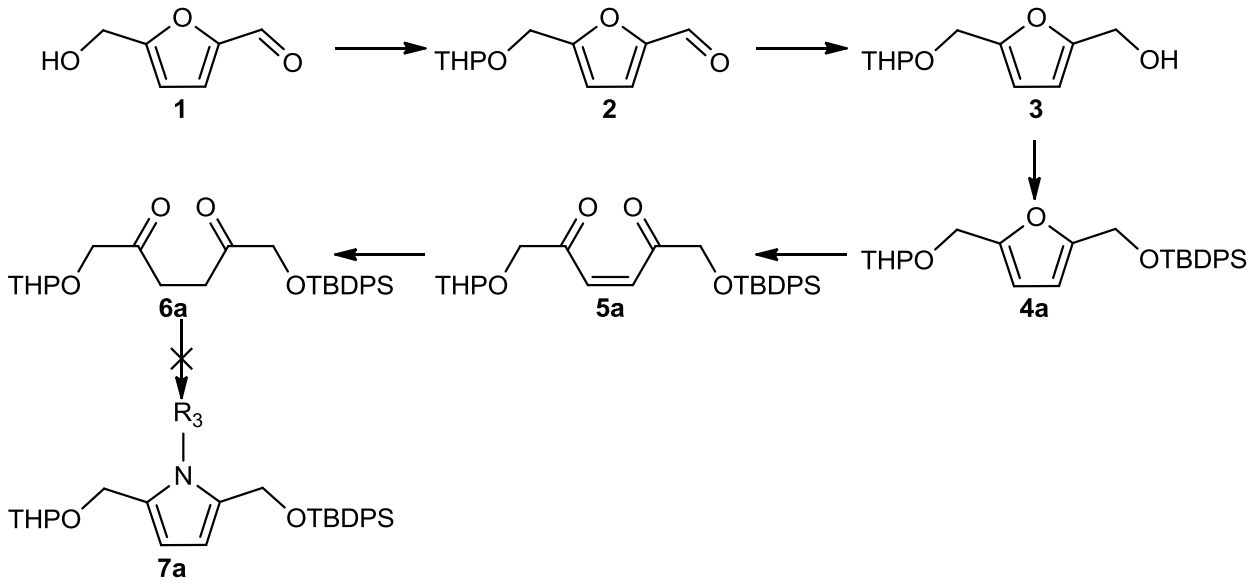



**Figure 2.3 Synthetic scheme using TBDPS protecting group**

The first attempts at synthesis involved the use of the tetrahydropyranyl ether (THPO) as $R_1$ and the *tert*-butyldiphenylsilyl ether (TBDPSO) as $R_2$ (Figure 2.3). The THPO protecting group is installed under acidic conditions, it is stable under the proposed reaction conditions, and is

removed by acid hydrolysis using *p*-toluenesulfonic acid in methanol.[32,33] Silyl ethers such as TBDPSO can be removed with tetra-*n*-butylammonium fluoride (TBAF).[32,34,35] Both protecting groups were stable under the oxidation of the furan and the reduction of the unsaturated bond; however, the Paal-Knorr pyrrole synthesis was unsuccessful. Each attempt resulted in recovery of at least 50% of the starting material and none of the desired pyrrole.

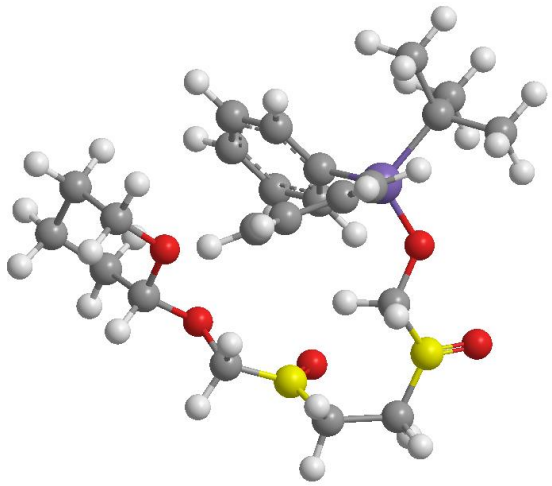


**Figure 2.4 Structure of the TBDPS saturated diketone (carbonyl carbons in yellow)**

It is possible that the bulky TBDPSO group causes steric hindrance, which prevents the formation of C-N bonds during the attempted pyrrole synthesis. The bulky nature of **6a** is presented in Figure 2.4. It is likely that the nitrogen of the amino acid is unable to position itself to bond with either of the carbonyl carbons.

## 2.3 The Use of Triethylsilyl Ether as the $R_2$ Group

The next synthetic method (Figure 2.5) involved the use of the triethylsilyl ether (TESO) protecting group. This group is stable under many of the same reaction conditions as TBDPSO,

but is significantly smaller than the TBDPSO group. Use of this group in the Paal-Knorr pyrrole synthesis could remove the steric hindrances that may prevent the reaction from taking place. The TES protecting group was successfully installed, but when MCPBA was used for the oxidative cleavage of the furan ring, none of the desired diketone was synthesized.

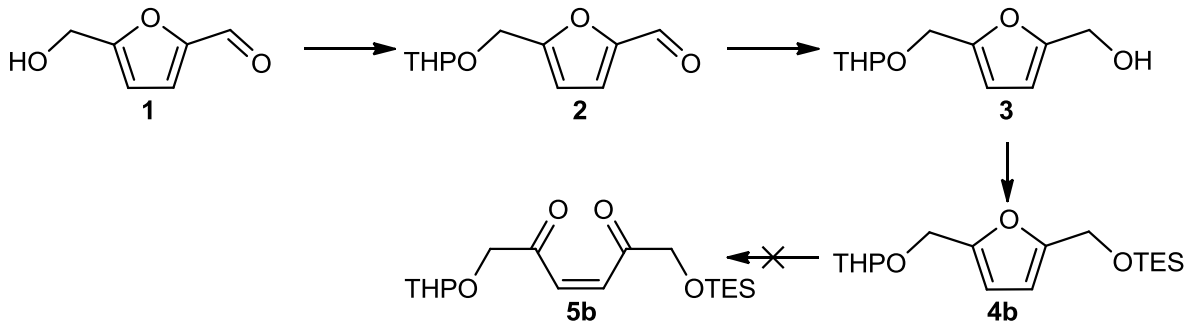



**Figure 2.5 Synthetic scheme using the TES protecting group**

When the products were separated using column chromatography, small amounts of **3** were recovered, along with the cleaved TES group, but none of the diketone was collected. Since TESO is not as stable in acidic conditions, it is likely that the mildly acidic MCPBA prevents the protecting group from staying intact.

2.4 Removal of TBDPS

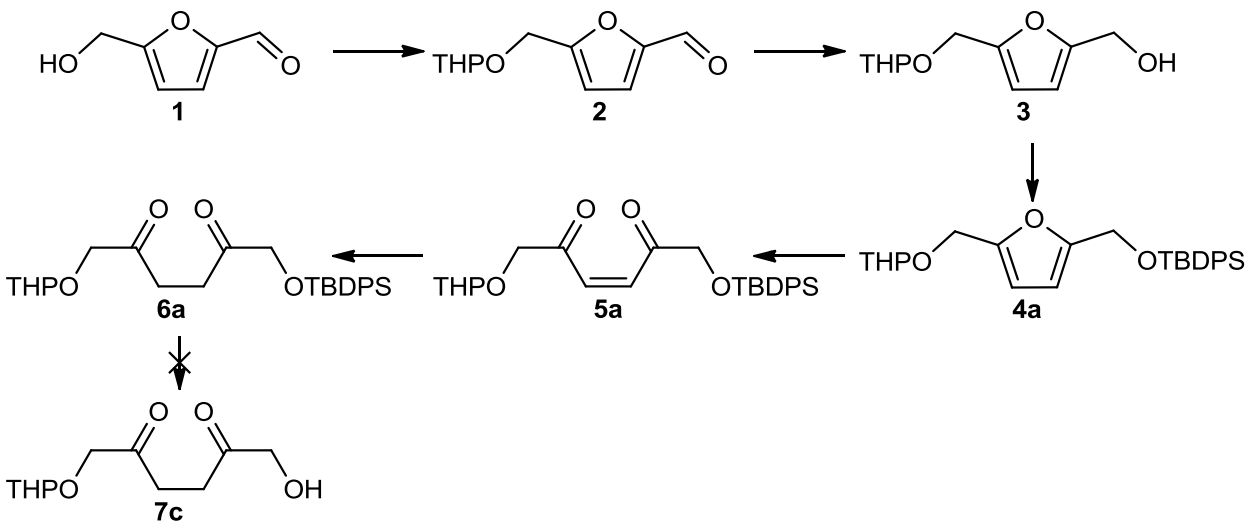



**Figure 2.6 Synthetic scheme cleaving TBDPS protecting group from the saturated diketone**

While the TESO group is not stable under the acidic/oxidation conditions, it is possible that that it would still be stable under the reaction conditions for the pyrrole synthesis. The next synthetic method that was attempted (Figure 2.6) involved combining the use of the TES and TBDPS ethers. The TBDPS ether would be used through the oxidation of the furan, and then replaced with TES for the pyrrole synthesis. The unsaturated diketone **6a** was treated with TBAF in order to remove the TBDPS. However, the reaction was unsuccessful under these conditions.

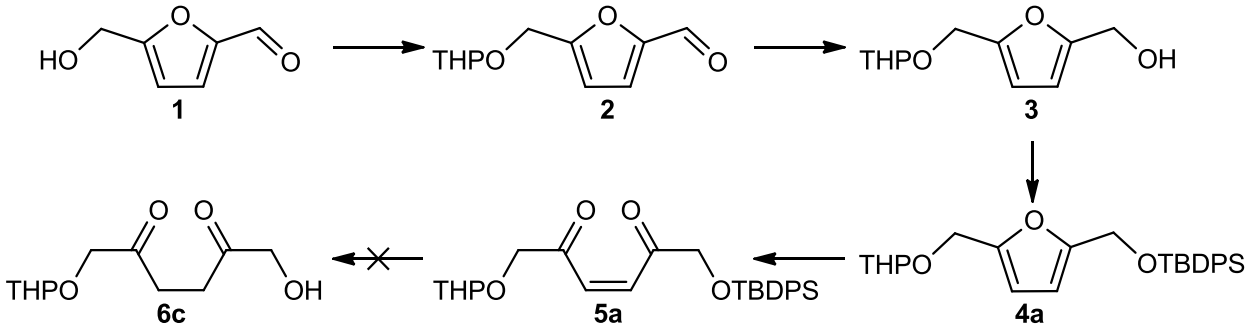



**Figure 2.7 Synthetic scheme cleaving TBDPS protecting group from the unsaturated diketone**

Next, the unsaturated diketone **5a** was treated with TBAF to remove the TBDPS at an earlier step, but there was no reaction (Figure 2.7). The increasing size of silyl ether protecting groups leads to an increase in resistance to both protection and deprotection.[36] While the TBDPS protecting group is stable under many reaction conditions, it is possible that the TBDPSO diketone is too resistant to hydrolysis.

## 2.5 The Use of Acetate Ester as the $R_2$ Group

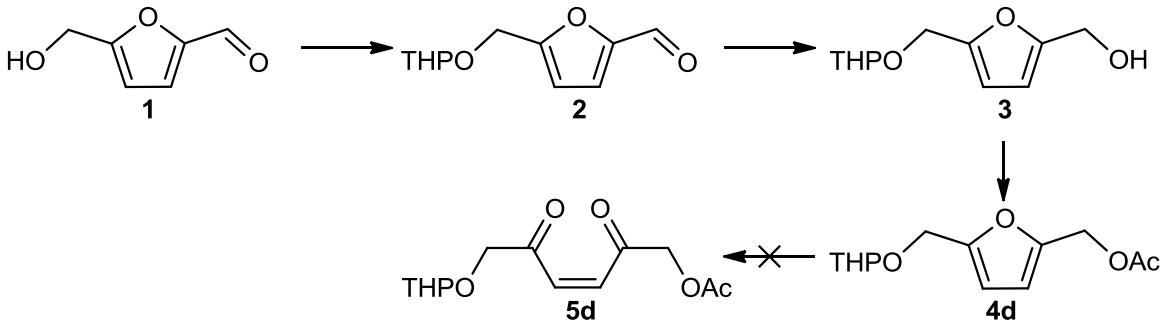



**Figure 2.8 Synthetic scheme using the acetate ester protecting group**

The third protecting group that was used in the original scheme (Figure 2.8) was the acetate ester (AcO). It is small like the TESO protecting group, but is also stable under highly acidic conditions. This protecting group is installed using acetic anhydride and triethyl amine in $CH_2Cl_2$. The installation of the acetate ether protecting group was successful, but when treated with MCPBA, there was no reaction.

2.6 The Use of Benzyl Ether as the $R_2$ Group

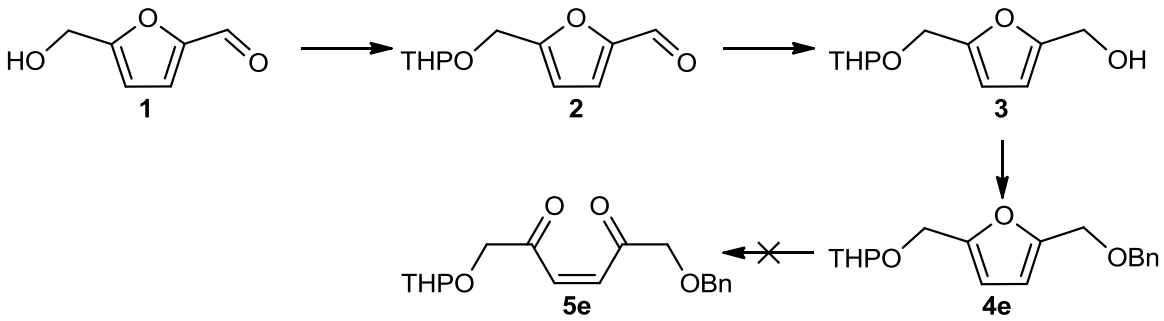



**Figure 2.9 Synthetic scheme using the benzyl ether protecting group**

The final protecting group used was the benzyl ether (BnO). This protecting group is smaller than TBDPSO, but still stable under many reaction conditions. The protecting group is attached under basic conditions with benzyl bromide and is removed with $H_2$ and palladium (Figure 2.9).[33,34] The BnO group was installed successfully, but was cleaved during the MCPBA oxidation.

# Chapter 3: Future Directions

## 3.1 The Maillard Reaction

While none of the attempts to synthesize the desired pyrrole alkaloids were completely successful, efforts are still being made in the synthesis of the desired compounds. One direction for this synthesis would involve a new synthetic scheme that begins with a Maillard Reaction. The Maillard Reaction, also known as "The Browning Reaction", is a reaction that occurs between amino acids and sugars such as glucose and xylose, which results in a variety of branched, heterocyclic compounds. There have been several reports of the use of glucose and amino acids to produce pyrroles similar to the target compounds in yields as high as 20%.[37–39] While this is a low yield, both of the starting materials are inexpensive. Therefore, development of a new scheme that begins with a Maillard Reaction may result in the synthesis of the desired pyrrole alkaloids in fewer steps and at a much lower cost.

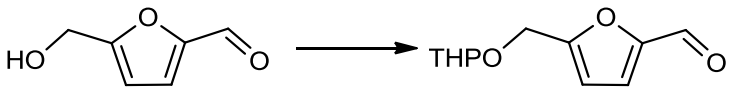
## 3.2 Biological and Stereochemical Interrogations

Once a method for synthesizing these pyrrole alkaloids is developed, further biological, stereochemical, and structure-activity interrogations can be performed. The synthesized compounds will have a known stereochemistry and by comparing their optical rotation and circular dichroism with those obtained for the isolated compounds, the stereochemical descriptors can be determined. After the stereochemistry of each isolate is determined, the next step will be to synthesize the remaining isomers. Once these compounds are obtained, the synthesis of novel pyrrole-alkaloids will be performed using additional amino acids. The

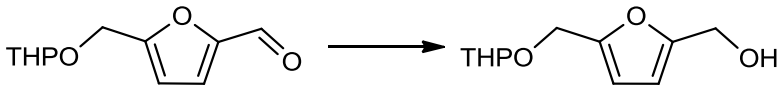
structure activity relationship will be investigated by comparing the biological activities of the isolated compounds and their synthetic derivatives.

Each compound synthesized will be biologically tested in order to determine their activity as potential chemopreventive agents. These compounds can be tested *in vitro* using the quinone reductase induction assay. The phase II enzyme NAD(P)H:quinone reductase can deactivate reactive species, such as radicals and electrophiles, that may disrupt normal cellular processes, and initiate carcinogenesis.[40] Compounds that prove to be active in this bioassay may then be tested further *in vivo* using the methods described in 2010 by G.D. Stoner et. al.[11] Any resulting leads could potentially be used to develop new cancer chemopreventive agents.

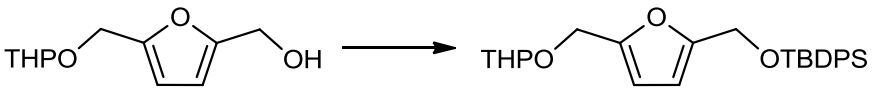
# Chapter 4: Experimental



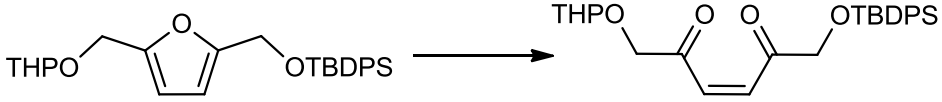

**5-(((Tetrahydro-2*H*-pyran-2-yl)oxy)methyl)furan-2-carbaldehyde (2)**. To a solution of 5-(hydroxymethyl)furfural (3.650 g, 28.96 mmol) in $CH_2Cl_2$ (60 mL) were added 3,4-dihydro-*2H*-pyran (3.17 mL, 34.7 mmol) and pyridinium *p*-toluenesulfonate (0.731 g, 2.91 mmol). The reaction mixture was stirred at room temperature for 2 h, then quenched with saturated $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic layer was then washed with brine (3 x 100 mL), dried with $MgSO_4$ and filtered. The filtrate was then concentrated *in vacuo* to yield compound **2** (5.793 g, 57.84 mL, 95%) as a pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 9.55 (s, 1H), 7.16 (d, 1H), 6.47 (d, 1H), 4.66 (d, 2H), 4.52 (d, 1H), 3.81 (t, 1H), 3.51 (d, 1H), 1.67 (m, 6H).



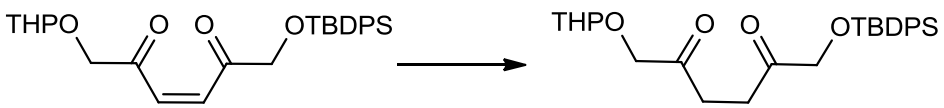

**(5-(((Tetrahydro-2*H*-pyran-2-yl)oxy)methyl)furan-2-yl)methanol (3)**. A solution of compound **2** (5.793 g, 27.55 mmol) in methanol (110 mL) was cooled to -10°C, then $NaBH_4$ (1.043 g, 25.55 mmol) was added, and the reaction mixture was stirred for 2 h at 0°C. After the reaction mixture was concentrated *in vacuo*, dissolved in $CH_2Cl_2$, washed with saturated $NaHCO_3$ (3 x 100 mL) and brine (3 x 100 mL), then the organic layer was dried with $MgSO_4$ and filtered. The filtrate was then concentrated *in vacuo* to yield compound **3** (5.695 g, 26.83 mmol, 97%) as a gold colored oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 6.15 (d, 2H), 4.62 (s, 1H), 4.53 (d, 1H), 4.44 (s, 2H), 4.35 (d, 1H), 3.79 (t, 1H), 3.46 (t, 1H), 1.60 (m, 6H).



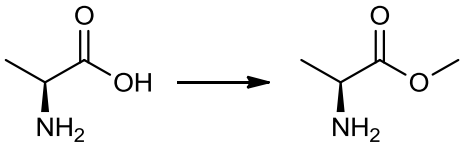

***tert*-Butyldiphenyl((5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)furan-2-yl)methoxy)silane (4a)**. To a solution of compound **3** (2.448 g, 11.53 mmol) in $CH_2Cl_2$ (65 mL), were added triethylamine (3.34 mL, 23.96 mmol), DMAP (0.145 g, 1.186 mmol), and TBDPSCl (3.71 mL, 14.26 mmol). After stirring at room temperature for 12 h, the solution was quenched with water (20 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic layers were then washed with saturated $NaHCO_3$ (3 x 100 mL) and brine (3 x 100 mL), then dried over anhydrous $MgSO_4$ and filtered. The filtrate was then concentrated *in vacuo* to yield compound **4a** (5.025 g, 10.72 mmol, 95%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 4H), 7.40 (m, 6H), 6.25 (t, 1H), 6.12 (t, 1H), 4.67 (m, 4H), 4.47 (m, 1H), 3.93 (m, 1H), 3.56 (m, 1H), 1.65 (m, 6H), 1.10 (s, 9H).



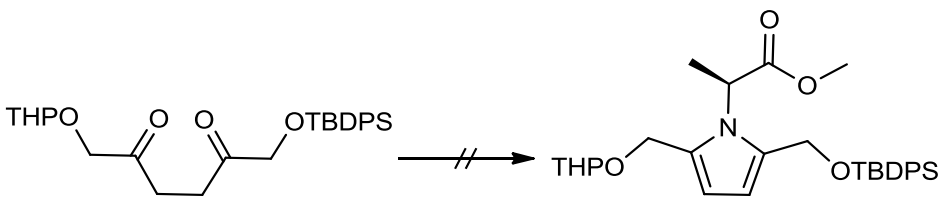

**(*Z*)-1-((*tert*-Butyldiphenylsilyl)oxy)-6-((tetrahydro-2*H*-pyran-2-yl)oxy)hex-3-ene-2,5-dione (5a)**. To a solution of compound **4** (5.277 g, 11.71 mmol) in anhydrous $CH_2Cl_2$ (40 mL) was added purified MCPBA (3.818 g, 22.12 mmol). The reaction mixture was stirred at room temperature, under argon gas, for 4 h, then filtered through a silica gel pad. The mixture was then washed with saturated $NaHCO_3$ (3 x 100 mL) and brine (3 x 100 mL), and then dried with anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* to yield compound **5a** (2.734 g, 5.859 mmol, 50%) as a pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.71 (m, 4H), 7.45 (m, 6H), 6.26 (d, 1H), 6.14 (d, 1H), 5.57 (s, 2H), 5.49 (q, 2H), 4.97 (s, 1H), 3.84 (t, 1H), 3.56 (t, 1H), 1.64 (m, 6H), 1.11 (s, 9H).




**1-((*tert*-Butyldiphenylsilyl)oxy)-6-((tetrahydro-2*H*-pyran-2-yl)oxy)hexane-2,5-dione (6a)**. To a solution of compound **5a** (0.255 g, 0.546 mmol) in acetic acid (5.46 mL) was added zinc powder (0.179 g, 2.74 mmol). The reaction was stirred at room temperature for 2 h, the zinc cake was filtered and washed with $CH_2Cl_2$. The filtrates were washed with saturated $NaHCO_3$ (3 x 100 mL) and brine (3 x 100 mL), then dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* to yield compound **6a** (0.1809 g, 0.389 mmol, 71%) as a pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.71 (m, 4H), 7.45 (m, 6H), 5.47 (s, 2H), 5.41 (s, 2H), 4.94 (t, 1H), 5.49 (q, 2H), 3.84 (m, 1H), 3.56 (m, 1H), 2.56 (m, 4H), 1.64 (m, 6H), 1.11 (s, 9H).




**D-Methyl 2-aminopropanoate**. A solution of D-alanine (0.497 g, 5.58 mmol) in methanol (5 mL) was stirred at -10°C, then $SOCl_2$ (0.59 mL, 8.2 mmol) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 2 h, then under reflux overnight. The volatiles were then concentrated *in vacuo* to yield D-methyl 2-aminopropanoate (0.575 g, 5.58 mmol, 100%) as an off-white solid, which was used without further purification. $^1$H NMR (300 MHz, $CDCl_3$): δ 4.27 (s, 1H), 3.81 (s, 3H), 2.42 (s, 2H), 1.72 (d, 3H).




**(*2S*)-Methyl2-(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-pyrrol-1-yl)propanoate (7a)**.

**Method A:** A solution of D-methyl 2-aminopropanoate (13.7 mg, 0.133 mmol) and triethylamine (0.019 mL, 0.13 mmol) in THF (0.16 mL) was stirred at room temperature for 20 min. To the solution were added compound **6a** (74 mg, 0.16 mmol) and iodine (34 mg, 0.27 mmol). The reaction was stirred for 24 h at room temperature, then $CH_2Cl_2$ (25 mL) was added and the mixture was washed with 0.1 M $Na_2S_2O_3$ (3 x 10 mL) and 0.5 M $NaHCO_3$ (3 x 10 mL), then dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* but compound **7a** was not formed.

**Method B:** A solution of D-methyl 2-aminopropanoate (7.4 mg, 0.072 mmol) and triethylamine (0.010 mL, 0.07 mmol) in THF (0.09 mL) was stirred at room temperature for 20 min. To the solution were added compound **6a** (40 mg, 0.085 mmol) and iodine (1.8 mg, 0.14 mmol). The reaction was stirred for 72 h at room temperature, then $CH_2Cl_2$ (25 mL) was added and the mixture was washed with 0.1 M $Na_2S_2O_3$ (3 x 10 mL) and 0.5 M $NaHCO_3$ (3 x 10 mL), then dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* but compound **7a** was not formed.

**Method C:** A solution of D-methyl 2-aminopropanoate (8.2 mg, 0.080 mmol) and triethylamine (0.011 mL, 0.079 mmol) in $CH_2Cl_2$ was stirred at room temperature for 20 min. To the solution

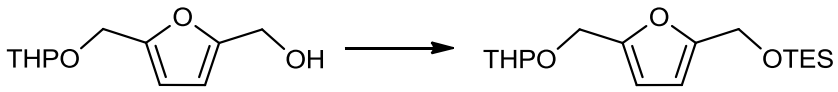
were added compound **6a** (40.5 mg, 0.096 mmol) and AcOH (0.023 mL, 0.40 mmol). The reaction was stirred for 72 h at room temperature then $CH_2Cl_2$ (25 mL) was added and the mixture was washed with 0.1 M $Na_2S_2O_3$ (3 x 10 mL) and 0.5 M $NaHCO_3$ (3 x 10 mL), then dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* but compound **7a** was not formed.

**Method D:** To a solution of D-methyl 2-aminopropanoate (8.8 mg, 0.086 mmol) in THF (0.0865 mL) were added compound **6a** (45.2 mg, 0.096 mmol) and iodine (2.2 mg, 0.017 mmol). The reaction was stirred for 12 h at room temperature, then $CH_2Cl_2$ (25 mL) was added and the mixture was washed with 0.1 M $Na_2S_2O_3$ (3 x 10 mL) and 0.5 M $NaHCO_3$ (3 x 10 mL), then dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* but compound **7a** was not formed.

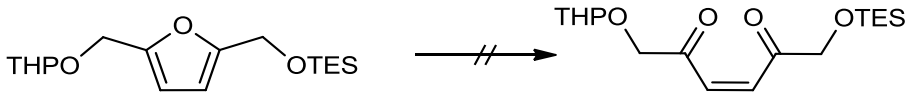
**Method E:** To a solution of D-methyl 2-aminopropanoate (10.8 mg, 0.11 mmol) in THF (0.106 mL) were added compound **6a** (56.0 mg, 0.11 mmol) and iodine (2.7 mg, 0.021 mmol). The reaction was stirred under reflux overnight, then $CH_2Cl_2$ (25 mL) was added and the mixture was washed with 0.1 M $Na_2S_2O_3$ (3 x 10 mL) and 0.5 M $NaHCO_3$ (3 x 10 mL), then dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* but compound **7a** was not formed.

**Method F:** To a solution of D-methyl 2-aminopropanoate (14.7 mg, 0.143 mmol) in $CH_2Cl_2$ (0.71 mL) were added compound **6a** (80.9 mg, 0.173 mmol) and AcOH (0.041 mL 0.723 mL). The reaction was stirred for under reflux for 4 h, then $CH_2Cl_2$ (25 mL) was added and the

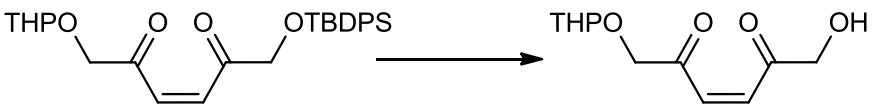
mixture was washed with saturated $NaHCO_3$ (3 x 10 mL) and brine (3 x 10 mL), then dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* but compound **7a** was not formed.



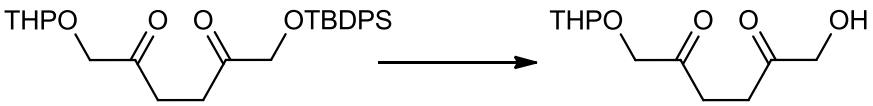

**Triethyl((5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)furan-2-yl)methoxy)silane (4b)**. To a solution of compound **3** (1.4715 g, 6.933 mmol) in $CH_2Cl_2$ (40 mL), were added triethylamine (1.88 mL, 13.4 mmol), DMAP (0.081 g, 0.66 mmol), and TESCl (1.35 mL, 8.04 mmol). After stirring at room temperature for 12 h, the solution was quenched with water (20 mL) and extracted with $CH_2Cl_2$. The combined organic layers were then washed with saturated $NaHCO_3$ (3 x 75 mL) and brine (3 x 75 mL), then dried over anhydrous $MgSO_4$ and filtered. The filtrate was then concentrated *in vacuo* to yield compound **4b** (2.128 g, 6.517 mmol, 94%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 6.21 (d, 1H), 6.15 (d, 1H), 4.67 (t, 1H), 4.57 (s, 2H), 4.42 (d, 2H), 3.66 (m, 1H), 3.50 (m, 1H), 1.59 (m, 6H), 0.92 (m, 9H), 0.60 (m, 6H).



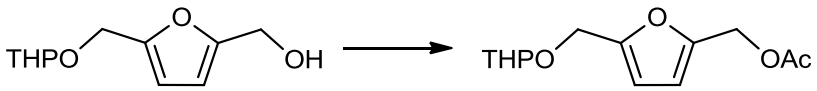

**(*Z*)-1-((Triethylsilyl)oxy)-6-((tetrahydro-2*H*-pyran-2-yl)oxy)hex-3-ene-2,5-dione (5b)**. To a solution of compound **4b** (1.8672 g, 5.72 mmol) in anhydrous $CH_2Cl_2$ (40 mL) was added purified MCPBA (1.8495 g, 10.71 mmol). The reaction mixture was stirred at room temperature, under argon gas for 4 h, then filtered through a silica gel pad. The mixture was then washed with saturated $NaHCO_3$ (3 x 75 mL) and brine (3 x 75 mL), then dried over anhydrous $MgSO_4$ and filtered. The filtrate was then concentrated *in vacuo* and loaded onto a silica gel column, but the product was not retrieved from the column.



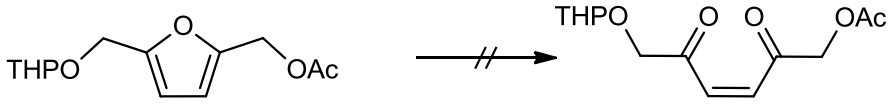

**(*Z*)-1-Hydroxy-6-((tetrahydro-2*H*-pyran-2-yl)oxy)hex-3-ene-2,5-dione (7c)**. A solution of compound **6a** (0.201 g, 0.428 mmol) in THF (4.5 mL) was stirred at 0°C for 15 min, then acetic acid (0.1 mL, 0.52 mmol) and TBAF (1.6 mL, 1.0 M in THF, 0.0016 mmol) were added and stirred at room temperature for 18 h, then washed with saturated $NH_4Cl$ solution (3 x 20 mL), extracted with $CH_2Cl_2$, and dried over anhydrous $MgSO_4$ and filtered. The filtrate was then concentrated *in vacuo* and loaded onto a silica gel column, but the product was not retrieved from the column.



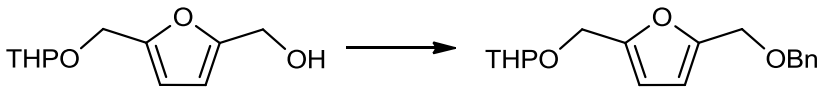

**1-Hydroxy-6-((tetrahydro-2*H*-pyran-2-yl)oxy)hexane-2,5-dione (6c)**. A solution of compound **5a** (0.177 g, 0.379 mmol) in THF (4.1 mL) was stirred at 0°C for 15 min, then acetic acid (0.08 mL, 1.19 mmol) and TBAF (1.1mL, 1.0 M in THF, 0.0011 mmol) were added and stirred at room temperature for 24 h, then washed with saturated $NH_4Cl$ solution (3 x 20 mL), extracted with $CH_2Cl_2$, then dried over anhydrous $MgSO_4$ and filtered. The filtrate was then concentrated *in vacuo* and loaded onto a silica gel column, but the product was not retrieved from the column.



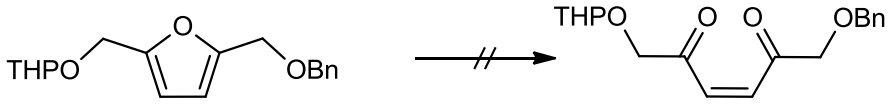

**(5-(((Tetrahydro-2*H*-pyran-2-yl)oxy)methyl)furan-2-yl)methyl acetate (4d)**. To a solution of compound **3** (0.501 g, 2.36 mmol) in $CH_2Cl_2$ (150 mL) were added triethylamine (5.26 mL, 37.8 mmol), acetic anhydride (5.13 mL, 54.3 mmol), and DMAP (0.018 g, 0.14 mmol). The reaction was stirred at room temperature for 2 h, and then quenched with methanol (50 mL). The mixture was diluted with $CH_2Cl_2$, washed with saturated $NaHCO_3$ (3 x 150 mL), dried with anhydrous $MgSO_4$, then filtered. The filtrate was then concentrated *in vacuo* to yield compound **4d** (0.562 g, 2.21 mmol, 94%) as a yellow colored oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 6.29 (d, 1H), 6.24 (d, 2H), 4.97 (s, 2H), 4.66 (s, 1H), 4.60 (d, 1H), 4.40 (d, 1H), 3.83 (m, 1H), 3.48 (m, 1H), 2.00 (s, 3H), 1.65 (m, 6H).




**(*Z*)-2,5-Dioxo-6-((tetrahydro-2*H*-pyran-2-yl)oxy)hex-3-en-1-yl acetate (5d)**. To a solution of compound **4d** (0.562 g, 2.21 mmol) in anhydrous $CH_2Cl_2$ (25 mL) was added MCPBA (0.573 g, 3.32 mmol). The reaction mixture was stirred at room temperature, under argon gas, for 4 h, and then filtered through a silica gel pad. The mixture was then washed with saturated $NaHCO_3$ (3 x 15 mL) and brine (3 x 15 mL), and then dried with anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* to yield and loaded onto a silica gel column, but the product (**5d**) did not elute from the column.




**2-((5-((Benzyloxy)methyl)furan-2-yl)methoxy)tetrahydro-2*H*-pyran (4e)**. To a solution of compound **3** (0.590 g, 2.78 mmol) in acetone (5 mL) was added potassium iodide (0.092 g, 0.56 mmol), potassium carbonate (0.576 g, 248.5 mmol), and benzyl bromide (0.36 mL, 3.1 mmol). The reaction was stirred at room temperature, overnight, then diluted with $CH_2Cl_2$, washed with saturated $NaHCO_3$ (3 x 15 mL) and brine (3 x 15 mL), and then dried with anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* to yield compound **4e** (0.722 g, 2.51 mmol, 90%) as a dark brown colored oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 5H), 6.26 (d, 1H), 6.22 (d, 1H), 4.71(t, 1H), 4.63 (d, 1H), 4.54 (s, 2H), 4.45 (d, 2H), 3.88 (m, 1H), 3.53 (m, 1H), 1.64 (m, 6H).




**(*Z*)-1-(Benzyloxy)-6-((tetrahydro-*2H*-pyran-2-yl)oxy)hex-3-ene-2,5-dione (5e)**. To a solution of compound **11** (0.512 g, 1.77 mmol) in anhydrous $CH_2Cl_2$ (20 mL) was added anhydrous MCPBA (0.461 g, 2.67 mmol). The reaction mixture was stirred at room temperature, under argon gas, for 4 hours, then filtered through a silica gel pad. The mixture was then washed with saturated $NaHCO_3$ (3 x 50 mL) and brine (3 x 50 mL), and then dried with anhydrous $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo* to yield and loaded onto a silica gel column, but the product did not elute from the column.

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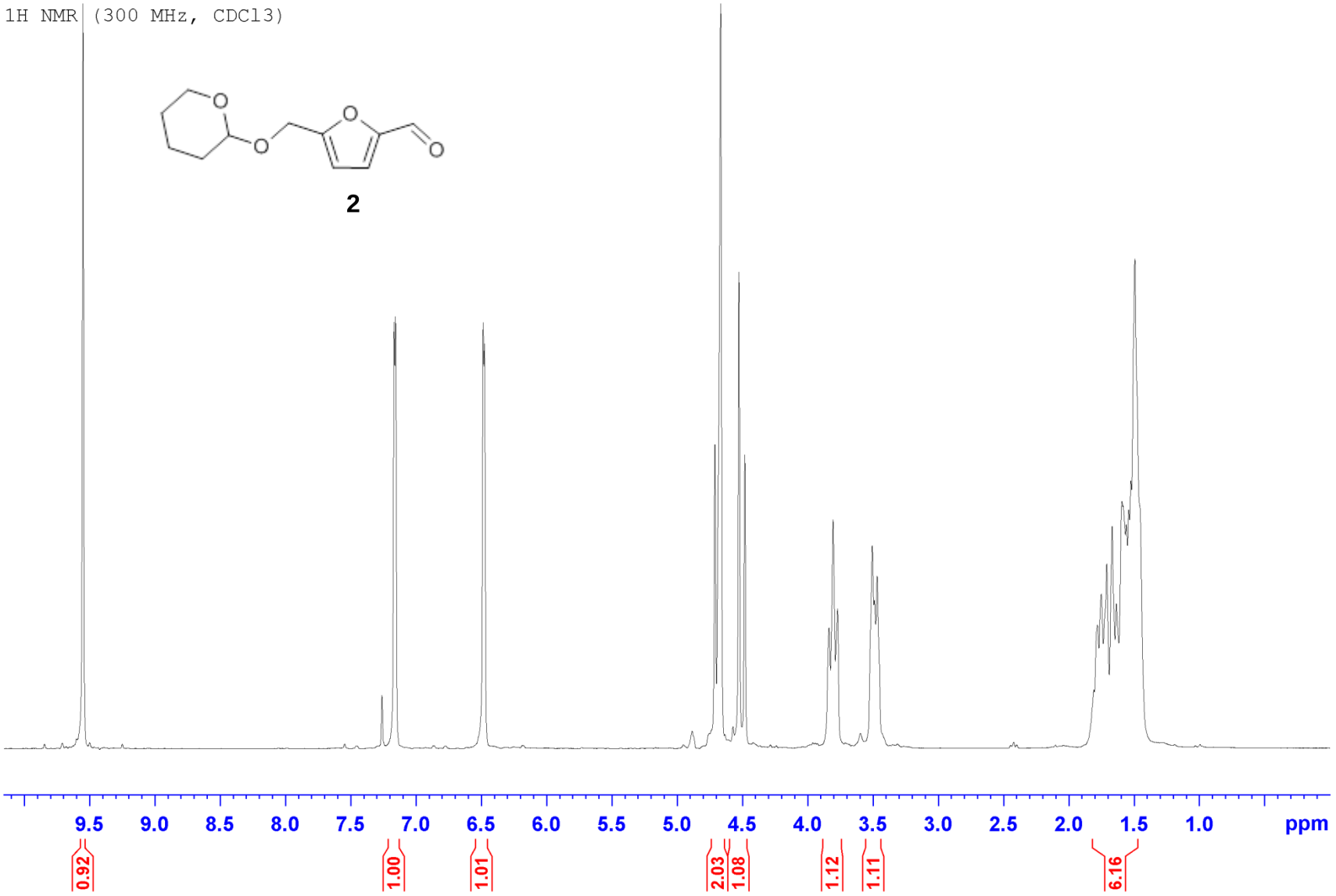
## Appendix: NMR Spectra of Selected Compounds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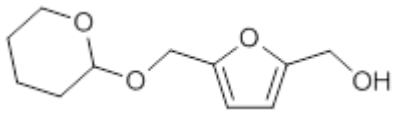
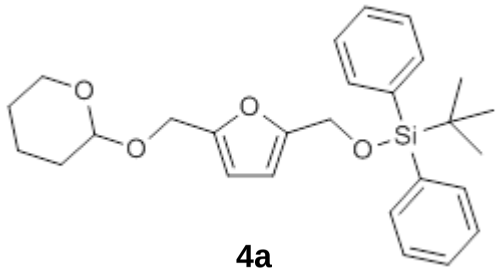
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.92
1.00
1.01
2.03
1.08
1.12
1.11
6.16

1H NMR (300 MHz, CDCl3)



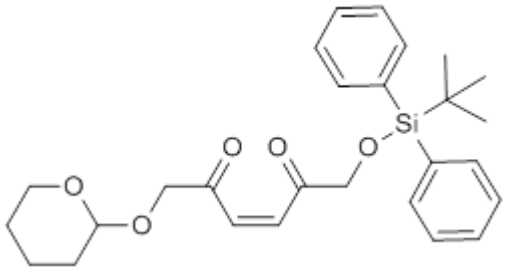

**3**

1H NMR (300 MHz, CDCl3)



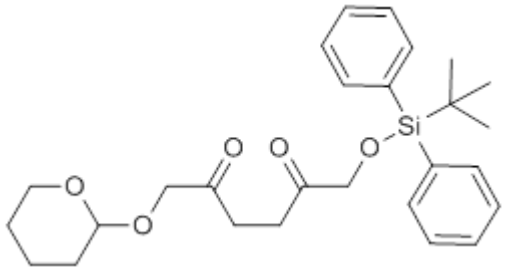

**4a**

1H NMR (300 MHz, CDCl3)



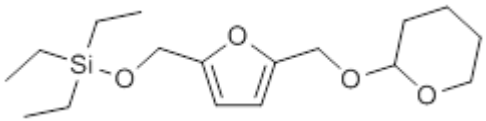

**5a**

1H NMR (300 MHz, CDCl3)



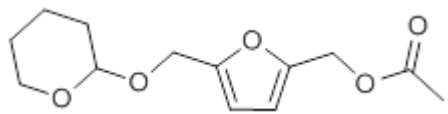

**6a**

1H NMR (300 MHz, CDCl3)



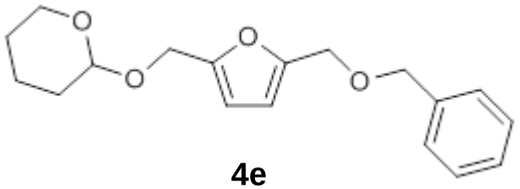

**4b**

1H NMR (300 MHz, CDCl3)



**4d**

1H NMR (300 MHz, CDCl3)



**4e**

**END**